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# Malaria makes the most of mealtimes

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**Successive synchronised cycles of *Plasmodium* replication in the host's blood causes the symptoms of malaria and fuels disease transmission. In this issue of *Cell Host & Microbe*, Hirako et al. (2018) reveal that host circadian rhythms of inflammation and metabolism are responsible for the timing of cycles of parasite replication.**

Periodicity of fever caused by the synchronised bursting of malaria (*Plasmodium*) infected red blood cells (every 24, 48, or 72 hours, depending on the parasite species) was discovered in the Hippocratic era and proved a useful diagnostic tool (Kwiatkowski & Greenwood 1989). Why natural selection has favoured parasites bursting at a particular time-of-day is unclear, but coordination with the circadian rhythms of both the host (O'Donnell et al. 2011) and vector (Schneider et al. 2018) appear to matter. Furthermore, how synchronized development is orchestrated across millions of parasites inside a host has been a mystery, until now. In this issue of *Cell Host & Microbe*, Hirako et al. (2018) reveal that the timing of developmental transitions during the asexual cycle is set by rhythms in the host inflammatory response that, in turn, regulates daily rhythms in blood glucose levels (Figure 1). Given that innate immune responses and altered glucose metabolism are fundamental features of many infectious diseases, Hirako et al.'s (2018) results may explain rhythms across malaria parasite species as well as the recently

discovered metabolic rhythms in Trypanosomes (Rijo-Ferreira et al. 2017).

To establish what drives malaria parasite rhythms, Hirako et al. (2018) followed a long and winding trail of observations. This required an extensive series of elegant experiments that integrates immunology with parasitology and chronobiology. They first demonstrated that peripheral blood mononuclear cells (PBMCs) from malaria patients exist in an altered metabolic state: the infected PBMCs exhibit an enriched gene signature for glucose metabolism. These findings were recapitulated in immune cells from mice infected with the rodent malaria *Plasmodium chabaudi*. These observations, coupled with many analogies between the infection dynamics of *P. chabaudi* and the most virulent human malaria species (*P. falciparum*) allowed Hirako et al. (2018) to use *P. chabaudi* as a model to probe connections between energy metabolism and parasite rhythms.

The host's circadian clock regulates inflammatory responses and metabolism, but infection can disrupt this regulation (Curtis et al. 2014). This prompted Hirako et al. (2018) to ask whether the expression of insulin response genes in immune cells - and in circulating glucose levels - is altered during malaria infection. They found that glucose homeostasis in wild-type mice is compromised by infection: blood glucose levels drop (hypoglycaemia) at the end of the active phase (dawn). For nocturnal mice, locomotor activity occurs at night, whereas the end of the active phase for humans corresponds to dusk. The authors note that in wild-type mice, parasites exist in the least glucose-demanding stage (the "ring" stage) when hosts are hypoglycaemic, completing the asexual cycle ("schizont" stage) and bursting during the night when blood glucose is high. Further, in mice unable to produce the proinflammatory cytokine interferon gamma (IFN $\gamma$ ), transcriptional signatures of insulin-responsive genes are altered in infected mice, hypoglycaemia is attenuated, and parasites lose synchrony.

The identification of another player, the pro-inflammatory cytokine Tumor Necrosis Factor (TNF $\alpha$ ), enabled connections to be made between IFN $\gamma$ , metabolic state, and parasites' rhythm.

Transcriptome analysis around the clock revealed daily oscillations in the expression of genes controlling glucose metabolism, including the insulin resistance pathway and TNF $\alpha$ . Notably, both TNF $\alpha$  expression and hypoglycaemia peak around dawn in *P. chabaudi*-infected mice.

Furthermore, IFN $\gamma$  is required for TNF $\alpha$  production and in TNF $\alpha$  deficient mice, hypoglycaemia at dawn is attenuated and parasites' rhythm is disrupted. Thus, Hirako et al. (2018) proposed that daily rhythms in TNF $\alpha$  expression regulate blood glucose levels and this sets the timing of parasite development during asexual replication. The critical support for their hypothesis came from time-restricted-feeding experiments. If mice are fed only in the daytime, the parasites' schedule shifts by 12hr and schizonts burst in the middle of the day, compared to when hosts eat only at night.

Additional experiments provided more evidence: the parasites' rhythm is lost in diabetic mice and the addition of glucose to drinking water for the same 6-hr period each day determines when bursting occurs. That the timing of development during the asexual cycle is determined by when hosts eat, not the host's light-dark schedule, also confirms findings in Prior et al. (2018), in which the appearance of the most glucose-hungry stage (schizont) coincides with food intake.

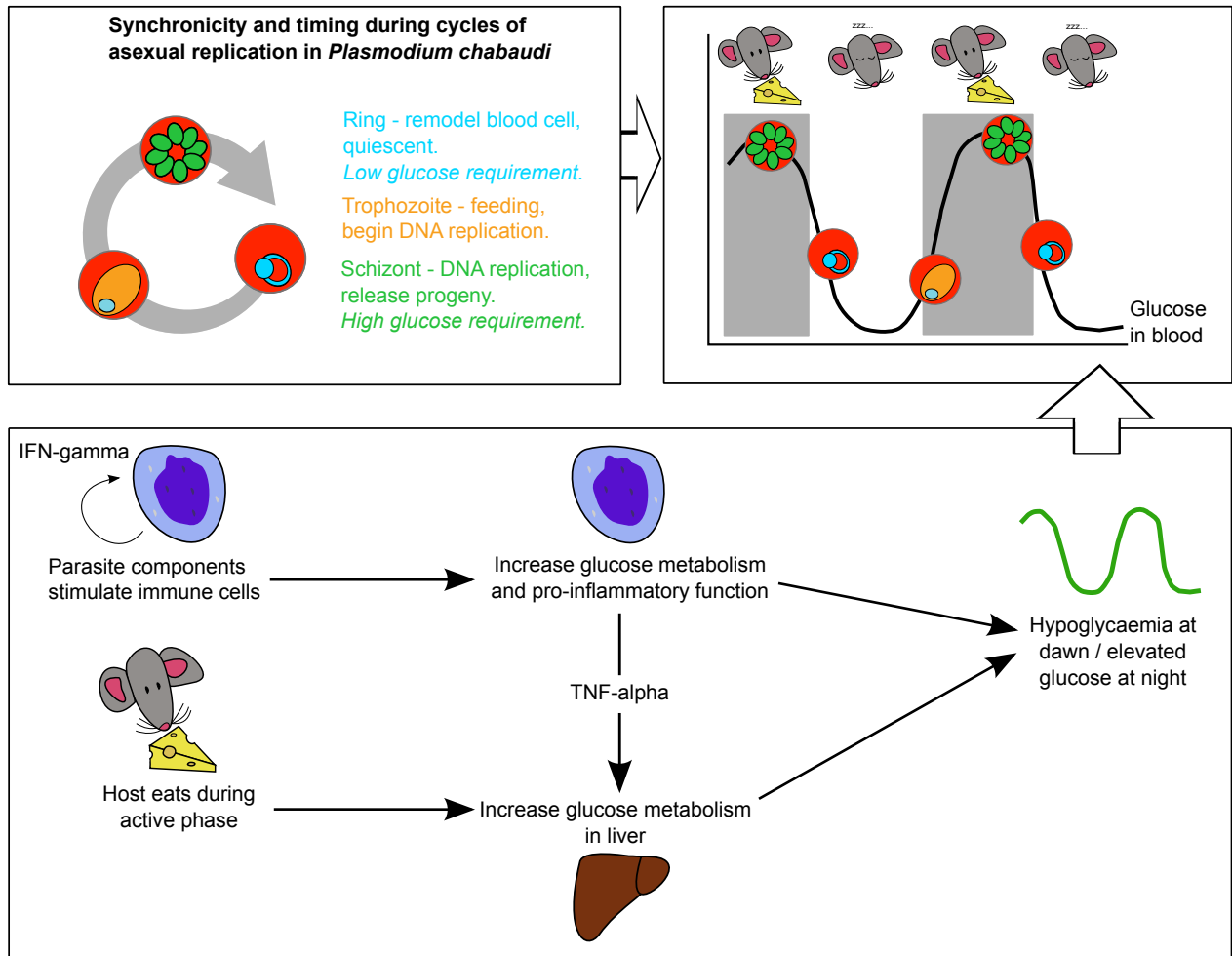
Hirako et al.'s (2018) findings overturn the dogma that host immune responses (particularly fever) generate parasite rhythms by killing certain development stages (particularly schizonts) at a certain time of day (Kwiatkowski & Greenwood 1989). Inflammatory cytokines do play well-established and important roles in killing parasites (Gazzinelli et al. 2014) and inflammation accompanies the synchronous bursting of schizonts. However, Prior et al. (2018) reveal that the timing of daily rhythms in inflammatory cytokines are a product, not a cause, of parasite rhythms, and Hirako et al. (2018) reveal that the role cytokines play in directing glucose metabolism matters. Yet, these observations suggest a conundrum. If synchronised bursting elicits an

immediate inflammatory response, shouldn't this affect the timing of host glucose metabolism and be sufficient to determine the timing of parasite development? Evidence suggests not: infections initiated with high numbers of synchronous parasites bursting at midday readily become rescheduled to the host's nocturnal feeding rhythm (O'Donnell et al. 2011). Given the tight coordination between host rhythms, perhaps the time of day that immune cells are stimulated does not affect the timing ("phase") of their resulting metabolic rhythms.

Is glucose a sufficiently limiting resource that parasites are unable to complete their asexual cycle until their host has eaten (analogous to how fever was thought to generate parasite rhythms)? If so, synchrony between parasites should be influenced by manipulations of host diet and parasite density. Alternatively, are parasites themselves responsible for setting the pace of their development in response to fluctuations in blood glucose? Parasites are rarely passive to changes in their within-host environment and observations suggest that they actively organise their schedule (Reece et al. 2017). For instance, malaria parasites have a nutrient sensing mechanism for glucose that dictates the number of progeny each parasite produces (Mancio-Silva et al. 2017). Perhaps parasites use this mechanism to glean time-of-day information from the host?

Hirako et al. (2018) provide insight on the role of inflammatory responses in malaria infection. That the timing of development during the asexual cycle is governed by a complex interaction between host metabolism and inflammation raises many new questions about how host-parasite interactions. First, if parasite development is limited by glucose availability, could TNF $\alpha$ -induced hypoglycaemia have evolved as a host defence to control infection? Second, do daily glucose rhythms also affect the pace of development of parasite species that require 2 or 3 days to complete development? Third, do parasites lose synchrony or become dormant during acute infection when hosts do not eat due to sickness? Finally, when innate responses are replaced by

adaptive responses (e.g., in chronic infections) is the timing of parasite development maintained by host feeding rhythms alone? The mechanistic insight provided by Hirako et al. (2018) makes these questions tractable.



**Figure 1. Timing of asexual replication in the malaria parasite *Plasmodium chabaudi* is determined by host circadian rhythms.** Inflammatory responses, especially TNF $\alpha$ , drive daily rhythms in blood glucose levels that generate rhythmicity in parasite development during the asexual cycle. Specifically, parasites exist in a quiescent stage when hosts enter their rest phase because hosts become hypoglycaemic, only transitioning to the most glucose-demanding stages and completing replication (schizogony) when hosts are in their active phase (regions with grey vertical bars) because feeding elevates blood glucose.

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